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ORIGINAL ARTICLE

The impact of a male or female thrombotic family history on contraceptive counseling: a cohort study

E. F. W. VAN VLIJMEN,* N. J. G. M. VEEGER,† S. MIDDELDORP,‡ K. HAMULYÁK,§ M. H. PRINS,¶ H. C. KLUIN-NELEMANS* and K. MEIJER*

*Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Center Groningen; †Department of Clinical Epidemiology, University Medical Center Groningen, Groningen; ‡Department of Vascular Medicine, Academic Medical Center Amsterdam, Amsterdam; §Department of Hematology, and Department of Clinical Epidemiology, Maastricht University Medical Center; and ¶Medical Technology Assessment, Maastricht University Medical Center, Maastricht, the Netherlands

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Essentials

- It is unknown if a male or female thrombotic family history influences risk in female relatives.
- We assessed thrombotic risk in female relatives of male and female patients with thrombosis.
- A hormonally related female thrombotic family history further increases risk in female relatives.
- This information could be important in counseling women on contraceptive options.

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Summary. *Background:* Women from thrombophilic families have increased risk of venous thromboembolism (VTE), which increases further during oral contraceptive (COC) use and pregnancy-postpartum. Whether this additional risk differs between relatives of male and female patients, or is different when that female patient had a hormonally related VTE (during COC use/pregnancy), is unknown. *Methods:* One thousand five female relatives of consecutive patients with VTE from a family-based cohort were retrospectively followed for incident VTE from ages 15 to 50, first VTE, or study inclusion. Absolute and relative VTE risks adjusted for factors of patients (sex, age) and relatives (thrombophilia, COC use,

pregnancy) were estimated in relatives of female and male patients and in relatives of female patients with and without hormonally related VTE. *Results:* Absolute risk in relatives of female (0.32 [95% confidence interval [CI] 0.23–0.43]) vs. male patients (0.39 [95% CI 0.28–0.53]) was comparable. However, the heterogeneity analysis of risk estimates suggested that in relatives of female vs. male patients, the contribution of pregnancy-postpartum (hazard ratio [HR] 11.6 [95% CI 6.3–21.3] vs. HR6.6 [95% CI 2.8–15.2]) and, to a lesser extent, COC use (HR3.6 [95% CI 1.8–7.1] vs. HR2.7 [95% CI 1.5–5.0]) to the VTE risk differs. Absolute risk was significantly higher in relatives of female patients with hormonally related VTE (0.43 [95% CI 0.3–0.6]) vs. relatives of female patients without hormonally related VTE (0.13 [95% CI 0.05–0.27]), HR3.28 [95% CI 1.5–7.9]). The higher contribution of pregnancy-postpartum and COC use to the VTE risk was mainly observed in relatives of patients with hormonally related VTE. *Conclusions:* These findings suggest that a family history from a female patient, especially when VTE was hormonally related, may further increase VTE risk in her female relatives. This information could be important in counseling women on contraceptive options.

Keywords: combined oral contraceptives; hereditary thrombophilia; venous thromboembolism.

Correspondence: Elizabeth van Vlijmen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands.
Tel.: +31 503612939; fax: +31 503611790
E-mail: e.f.w.van.vlijmen@umcg.nl

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Introduction

There are many factors that contribute to the individual baseline risk of venous thromboembolism (VTE). Hereditary thrombophilia and first-degree family history are both established independent risk factors [1–4]. The baseline risk can be further increased by underlying conditions like cancer and obesity, by exogenous risk factors such as surgery and trauma, and, in women of reproductive age,

by the use of combined oral contraceptives (COCs) and the pregnancy-postpartum period [5]. Recent studies indicate that exposure to hormone factors plays a decisive role in the development of VTEs in women during the reproductive age. Adjustment for reproductive risk factors was reported to reduce risk of VTE in women of reproductive age to half of that in men of the same age [6].

Previously, we studied the contribution of hormone exposure (i.e., COC use and pregnancy-postpartum) to the baseline risk of VTE in female relatives of patients with VTE from families with mild (factor V [FV] Leiden and prothrombin G20210A mutation) and severe hereditary thrombophilia (antithrombin, protein C, and protein S deficiency) [7–9]. It was shown that in female relatives of reproductive age with thrombophilia the risk of VTE was further increased during hormone exposure, of which the impact was highest in women with severe thrombophilic defects. Additionally, in these cohorts of female relatives of patients with VTE, who per definition all had a positive family history, those without thrombophilia also had a higher risk of VTE during hormone exposure than reported in the general population [7,8]. This is in line with publications indicating that family history is an independent risk factor, regardless of other risk factors present [4]. It is unknown whether this family-conferred risk is hormone or sex specific: is a young woman at higher hormone-related risk if her mother or sister had COC- or pregnancy-related VTE than if her father or brother had thrombosis? This would be relevant for counselling purposes.

In order to investigate this question, we have included in the present study the first-degree female relatives of reproductive age of consecutive patients with VTE and hereditary thrombophilia from our thrombophilic family cohorts. As all patients had experienced VTE, all female relatives had an established positive family history of VTE. This provided us with the unique opportunity to evaluate in these female relatives the impact of a family history originating from a male or female patient and to investigate whether a positive family history originating from a female patient with a VTE during hormone exposure (during COC use or pregnancy) has an additional impact on their risk profile. For this purpose, we estimated absolute and relative risk of VTE in female relatives of male patients, of female patients with hormonally related VTE, and of female patients without hormonally related VTE.

Methods

Subjects

In the present family-based cohort study, female relatives from consecutive patients (proband) with VTE were included from five cohorts of thrombophilic families from three university hospitals in the Netherlands, which were described in detail elsewhere [1–3]. The first cohort was single-center study of first-degree relatives of consecutive

proband with VTE and antithrombin, protein C, or protein S deficiency. As the number of antithrombin deficient probands was small, second-degree relatives with a deficient parent were also identified. Enrollment took place from 1999 to 2004. Three multicenter studies included first-degree relatives of consecutive probands with VTE or premature atherosclerosis (< 50 yrs) and prothrombin-G20210A, high FVIII levels (150 IU dL⁻¹), or hyperhomocysteinemia, respectively. The fifth study was a multicenter study, which included first-degree relatives of probands with VTE and an FV Leiden mutation. These relatives were enrolled between 1995 and 1998 (FV Leiden study) and 1998 and 2004 (prothrombin-G20210A, hyperhomocysteinemia, and FVIII studies) at three university hospitals in the Netherlands. Proband were excluded to avoid bias, as they have experienced VTE by definition. Relatives of probands with premature atherosclerosis were not included in the present study. In these cohorts, only hereditary thrombophilic defects were taken into account; a high FVIII level and hyperhomocysteinemia are not considered hereditary thrombophilic defects (Fig. 1). Strategies applied for collection of information on exposure to exogenous risk factors for VTE, including contraceptive use and pregnancies (including pregnancy losses), are described in detail in our previous studies based on these cohorts [7–9]. Relatives were queried about exposure to VTE risk factors and VTE occurrence from time point of study inclusion back to the age of 15. For the present cohort study, all data collected on hormone exposure and risk factors present at time of VTE of the probands were confirmed by review of the probands' medical files. All relatives had given informed consent, and the original study cohorts were approved by the institutional review boards of the three participating Dutch hospitals (University Medical Centers of Groningen, Amsterdam, and Maastricht).

Person-years of exposure were counted from age 15 until 50 years, first VTE, or end of study. A minimum age of 15 years was chosen because VTE occurrence below this age is rare, and a maximum age of 50 years was chosen as the end of fertile lifetime. The duration of exposure to COCs (years of COC use) included actual use including a 3-month exposure window after COC use was discontinued. For pregnancy, including pregnancy losses, exposure was defined as the gestation time plus 3-month postpartum.

Diagnosis of VTE

VTE was considered established when diagnosed by compression ultrasound or venography (deep vein thrombosis), ventilation/perfusion lung scan, spiral computed tomography scan, or pulmonary angiography (pulmonary embolism) or when the patient had received full-dose heparin and vitamin K antagonists for at least 3 months without objective testing at a time when these techniques

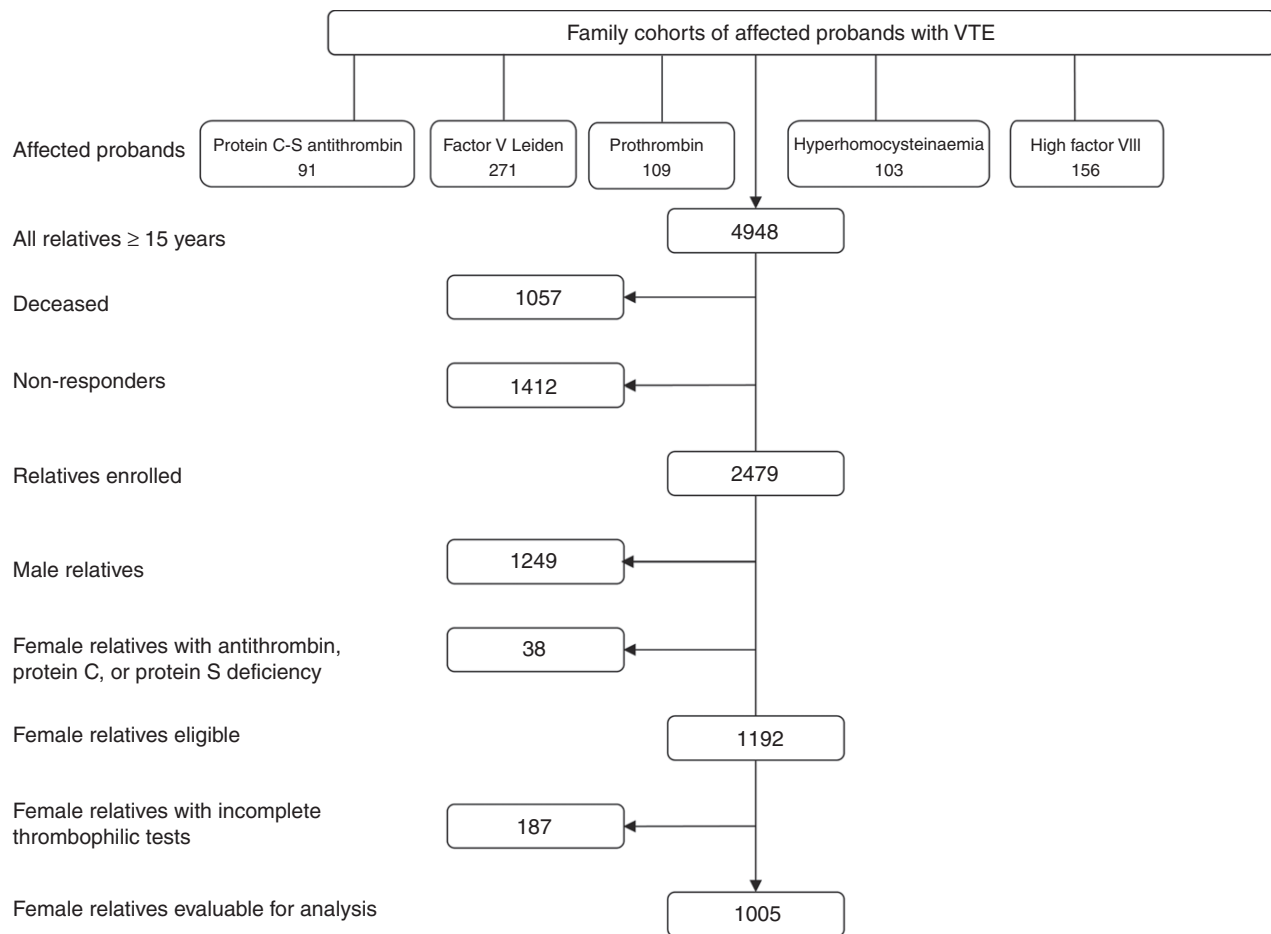


Fig. 1. Recruitment of patients (proband) with venous thromboembolism (VTE) and first-degree female relatives.

were not available. VTE was classified as 'provoked' when occurring up to 3 months after exposure to exogenous risk factors, which included surgery, trauma, immobilization for at least 7 days, COC use, pregnancy-postpartum up to 3 months, and malignancy.

In the absence of these risk factors, VTE was defined as 'unprovoked.' Superficial phlebitis was not considered a thrombotic event [1–3].

Laboratory studies

FV Leiden and prothrombin-G20210A mutation were demonstrated by polymerase chain reaction [10,11]. Protein S- and protein C-Ag levels were measured by ELISA (DAKO, Glostrup, Denmark); protein C activity and antithrombin levels (Chromogenix, Mölndal, Sweden) were measured by chromogenic substrate assays.

Normal ranges were determined in healthy volunteers without a (family) history of VTE, who were neither pregnant nor used COCs within 3 months before blood sampling. Deficiency of antithrombin, protein S, and protein C was defined by levels below the lower limit of their normal ranges.

In probands and symptomatic relatives, blood samples were collected at least three months after VTE had occurred. If they were still treated with vitamin K antagonists, samples were taken after temporary change of this therapy to low molecular weight heparin for at least 2 weeks [1–3].

Statistical analysis

VTE risk estimation We estimated the overall absolute risk of VTE in this cohort, as well as absolute VTE risk in female relatives originating from a female vs. a male patient (proband). The absolute risk was expressed as the incidence rate (IR) per 100 person-years, with 95% confidence intervals (CIs). Their person-years of exposure were counted from age 15 until age 50, first VTE, or the end of study (time of inclusion).

Relative risks were estimated using Cox regression analysis. Testing proportionality (i.e., the proportional hazard assumption) was part of the survival analysis. The proportionality assumption was assessed by including an interaction with event time in the model. To account for time-varying exposures of COC use and

pregnancies, an extended Cox model (with time-varying exposures) was used. In this multivariable model, hazard ratios (HRs) of female vs. male proband, age of the proband at time of first VTE (< 45 yrs vs. \geq 45 yrs), COC use vs. no use, pregnancy-postpartum vs. no pregnancy, and presence of thrombophilia vs. no thrombophilia were estimated. Possible effect modification (interactions) of mild or severe thrombophilic defects on risk of COC use and pregnancy-postpartum were also taken into account.

Further, within the group of female relatives originating from a female proband, absolute and relative risk estimations as described earlier were calculated for the female relatives with a female proband with hormonally related VTE (VTE during COC use or pregnancy-postpartum) vs. female relatives with a female proband without hormonally related VTE.

Because this is a family-based study, all relative risk estimations were also adjusted for clustering within families.

Continuous variables were expressed as mean values and standard deviation (SD) or median values and range, and categorical data as counts and percentages. A two-sided *P*-value of < 0.05 indicated statistical significance. Analyses were performed using SAS software, version 9.4 (SAS Institute., SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics of probands and their female relatives

The original cohorts consisted of 730 thrombophilic patients (proband) with VTE. The flow chart, presented in Fig. 1, displays the number of relatives of these probands who could not be enrolled, which included non-responders (no consent, geographical distance) and relatives who were deceased. In total, 1230 relatives were female. After excluding female relatives in whom inheritance of the index defect could not be established, and those who had incomplete thrombophilia testing, 1005 female relatives were available for analysis, originating from 465 probands.

The upper part of Table 1 presents the characteristics of the probands, divided into male and female probands of whom the latter group is divided further into female probands with or without a hormonally related VTE. Characteristics of the probands in these three groups were comparable with regard to hormone exposure (COC use and pregnancy-postpartum), but probands with hormonally related VTE had their first VTE at considerably younger median age (i.e., 26.5 yrs) than female probands without hormonally related VTE (44.0 yrs) and male probands (45.0 yrs).

The lower part of Table 1 presents the characteristics of the 1005 female relatives of these probands, of whom

604 originated from a female proband and 401 from a male proband. Of the 604 relatives of female probands, 394 originated from female probands with hormonally related VTE and 206 from female probands without hormonally related VTE. For four relatives (who experienced no VTE during follow-up), the female probands' hormone exposure at the time of VTE was unknown. The characteristics did not differ strongly between relatives of male proband and the two female proband groups. Deep vein thrombosis (DVT) was diagnosed in the majority of VTE cases, and the proportions of DVT, PE and other VTE are comparable between relatives of male and female probands. However, in the relatives with a VTE, a median duration of COC use of 0.46 year up to time of VTE was considerably shorter in relatives of female probands with hormonally related VTE than in female relatives of female probands without hormonally related VTE (5 yrs) and female relatives of male probands (4 yrs).

VTE risk in female relatives of female vs. male probands

Follow-up in female relatives covered 24.195 person-years with 84 VTEs, of which 82% was related to COC use or pregnancy-postpartum. Crude absolute VTE risk was 0.35 (95% CI 0.28–0.43) per 100 person-years.

As presented in Table 2, the risk in relatives of female (0.32, 95% CI 0.23–0.43) vs. male probands (0.39, 95% CI 0.28–0.53) was comparable, but young age (< 45 yrs at time of first VTE) of the proband, and presence of thrombophilia, COC use, and pregnancy of the relative were factors that significantly increased risk of VTE. In the multivariable analysis, thrombophilia, COC use, and pregnancy of relative, but not probands' age, remained independent risk factors.

However, the heterogeneity analysis of risk estimates for relatives of male vs. female probands showed a substantially higher pregnancy-related risk of VTE (HR 11.6 [95% CI 6.3–21.3]) in relatives of female probands than in relatives of male probands (HR 6.6 [95% CI 2.8–15.2]), although the formal test for interaction between pregnancy and sex of proband was not significant (*P* = 0.39). For COC use, the difference in increased risk of VTE was less pronounced, that is, HR 3.6 (95% CI 1.8–7.1), in relatives of female probands vs. HR 2.7 (95% CI 1.5–5.0) in relatives of male probands (Table 3).

VTE risk in female relatives of female probands with or without hormonally related VTE

When taking hormone exposure of the proband at the time of VTE into account, the incidence rate (IR) of VTE was significantly higher, that is, IR 0.43 (95% CI 0.31–0.59) per 100 person-years in relatives of probands with hormonally related VTE, than noted in relatives of female

Table 1 Clinical characteristics of male and female probands* with or without hormonally related VTE and their 1005 first-degree female relatives

	Male probands	All female probands	Female† probands with hormonally related VTE	Female† probands without hormonally related VTE
Probands*, <i>n</i>	179	286	195	91
Ever COC users, %	NA	66.0	85.6	68.1
Ever pregnant, %	NA	70.2	68.0	76.9
Ever pregnant + ever COC use %	NA	56.1	56.0	56.2
Age (IQR) at time of VTE, yrs	46 (35–55)	32 (24–44)	27 (22–38)	44 (34–52)
Female relatives‡, <i>n</i>	401	604	394	206
Thrombophilia	179 (45)	306 (52)	198 (50)	70 (34)
Mild thrombophilic defects§, <i>n</i> (%)	111 (28)	209 (35)	113 (29)	48 (23)
Severe thrombophilic defects¶, <i>n</i> (%)	68 (17)	107 (18)	85 (22)	22 (11)
Total follow-up, yrs**	9.757	14.438	9.014	5.299
Ever COC users, <i>n</i> (%)	285 (71)	428 (71)	280 (71)	145 (70)
Total number of pill yrs	2173	3340	1941	1360
Duration of use	3.56	3.26	2.76	4.78
Ever pregnant, <i>n</i> (%)	283 (71)	407 (67)	258 (66)	145 (70)
Total number of pregnancy yrs	759	1073	687	378
Pregnancy time, yrs	2.0	2.0	1.9	2.0
Age (IQR) at time of VTE, yrs	28 (24–35)	26 (22–31)	26 (22–31)	26 (19–31)
VTE, <i>n</i>	38	46	39	7
Type of VTE				
DVT	26	29	26	3
PE	8	10	6	4
DVT + PE	1	3	3	–
Other	3	4	4	–
VTE without hormone exposure	9	6	5	1
VTE during COC use	15 (40)	19 (41)	15	4
Duration COC use, yrs	4.0		0.46	5.3
VTE during pregnancy/postpartum	14 (37)	21 (46)	19	2

COC = combined oral contraceptive; NA = data not applicable; VTE = venous thromboembolism. Data are given as median unless otherwise indicated. *Probands: patients with established VTE. †In one female proband information on exposure hormone exposure at time of VTE was unknown; therefore, her four relatives (who experienced no VTE during follow-up) were excluded. ‡Relatives: first-degree relatives of the probands. §Mild thrombophilic defects: factor V Leiden or prothrombin G20210A mutation. ¶Antithrombin, protein C, or protein S deficiency, including 47 (4.7%) women who were heterozygous for both factor V Leiden and prothrombin G20210A mutation and women who were homozygous for factor V Leiden or prothrombin G20210A mutation. **Observation years in female relatives restricted to time between age 15 and 50 yrs.

probands without hormonally related VTE (IR 0.13 [95% CI 0.05–0.27], HR 3.3 [95% CI 1.5–7.9]; $P = 0.011$).

When considering only relatives of female probands, the noted heterogeneity with the higher HRs of pregnancy and, to a lesser extent, COC use (Table 3) is mainly observed in the relatives of female probands with a hormonally related VTE. The risk estimates in relatives of female probands without hormonally related VTE were substantially lower (Table 4). An overview of all crude incidence rates is presented in the Table S1.

Discussion

In this large cohort study of first-degree female relatives of thrombophilic patients with VTE, which evaluated possible sex- and hormone-specific aspects in family history, the overall absolute risk of VTE was not significantly different between female relatives of male or female patients. However, extended Cox regression analyses showed that the contribution of pregnancy-postpartum to the risk of

VTE was almost double in female relatives of female patients (HR 11.6) compared with female relatives of male patients (HR 6.6), although not significant ($P = 0.39$). When considering only relatives of female patients, the noted heterogeneity in the contribution of pregnancy and to a lesser extent COC use to the risk of VTE is mainly observed in relatives of patients with a hormonally related VTE. This difference is also reflected by the 3-fold higher absolute risk in female relatives of female patients with hormonally related VTE (HR 3.3, 95% CI 1.5–7.9; $P = 0.011$). The observed heightened risks suggest that female relatives of patients with hormonally related VTE are more susceptible to hormone exposure.

Several studies have explored the impact of positive family history and it is considered an independent risk factor of VTE with reported odds ratios varying between 2.2 and 2.7 [4,12,13]. Additionally, two studies have reported the VTE risk of a positive family history as higher in female relatives during fertile age than in male relatives of that age [14,15].

Table 2 Crude HRs with corresponding incidence rates and adjusted HRs in female relatives of all probands

Variable*	Crude HR† (IR)	Adjusted HR†
Relatives of female vs. male probands*‡	0.8 (0.5–1.3, $P = 0.42$) (0.32 [0.23–0.43] vs. 0.39 [0.28–0.53])	–
Relatives of probands aged < 45 yrs vs. probands aged ≥ 45 yrs at time of first VTE*‡	1.8 (1.0–3.2, $P = 0.045$) (0.42 [0.11–0.31] vs. 0.23 [0.14–0.36])	–
Relatives with mild thrombophilia vs. no thrombophilia*‡,§	3.2 (1.8–5.6, $P < 0.0001$) 0.35 [0.22–0.52] vs. 0.14 [0.08–0.21])	3.4 (1.9–6.0)
Relatives with severe thrombophilia vs. no thrombophilia*‡,§	10.4 (5.8–18.6, $P < 0.0001$) (1.22 [0.66–1.65] vs. 0.14 [0.08–0.21])	11.2 (6.1–20.7)
COC use vs. no COC use*‡,§	1.9 (1.2–3.1, $P = 0.008$) (0.62 [0.43–0.86] vs. 0.27 [0.20–0.35])	3.2 (2.1–5.0)
Pregnancy vs. no pregnancy*‡,§	7.4 (4.2–12.9, $P < 0.0001$) (1.91 [1.35–2.63] vs. 0.22 [0.16–0.29])	9.0 (5.3–15.1)

HR = hazard ratio; IR = incidence rate. Mild thrombophilia: factor V Leiden or prothrombin G20210A mutation. Severe thrombophilia: antithrombin, protein C, or protein S deficiency, and double heterozygous, or homozygous factor V Leiden or prothrombin G20210A mutation. Probands: patients with established VTE. *Incidence rates are presented in the Table S1. †Adjusted for clustering within families. ‡Variables included in the initial univariable analysis. §Variables included in the final multivariable analysis.

Table 3 Adjusted HRs of mild or severe thrombophilia, COC use, and pregnancy in female relatives of male and female probands

Variable*	HRs† in relatives of male probands	HRs† in relatives of female probands
Mild thrombophilia vs. no thrombophilia‡	3.2 (1.3–7.8)	3.4 (1.6–7.4)
Severe thrombophilia vs. no thrombophilia‡	13.0 (5.2–32.6)	10.2 (4.4–23.7)
COC use vs. no COC use‡	2.7 (1.5–5.0)	3.6 (1.8–7.1)
Pregnancy vs. no pregnancy‡	6.6 (2.8–15.2)	11.6 (6.3–21.3)

HR = hazard ratio. Mild thrombophilia: factor V Leiden or prothrombin G20210A mutation. Severe thrombophilia: antithrombin, protein C, or protein S deficiency, and double heterozygous, or homozygous factor V Leiden or prothrombin G20210A mutation. Probands: patients with established VTE. *Incidence rates are presented in the Table S1. †Adjusted for clustering within families. ‡Variables included in the multivariable analysis.

To our knowledge, only one study has evaluated sex of patient as one of the potential predictors of VTE risk in their first-degree relatives. The authors reported highest VTE risk in relatives of patients with unprovoked VTE and in relatives of patients who had VTE at younger age (< 45 yrs), whereas sex of patient was no significant risk

Table 4 Adjusted HRs of mild or severe thrombophilia, COC use, and pregnancy in female relatives of female probands with and without hormonally related VTE

Variable*	HRs† in relatives of female probands with hormonally related VTE	HRs† in relatives of female probands without hormonally related VTE
Mild thrombophilia vs. no thrombophilia‡	3.7 (1.5–9.2)	1.5 (0.2–9.0)
Severe thrombophilia vs. no thrombophilia‡	10.5 (3.9–28.0)	4.0 (0.4–43.0)
COC use vs. no COC use‡	3.3 (1.6–7.1)	4.6 (1.0–21.5)
Pregnancy vs. no pregnancy‡	12.2 (6.3–23.8)	7.3 (1.4–38.1)

HR = hazard ratio. Mild thrombophilia: factor V Leiden or prothrombin G20210A mutation. Severe thrombophilia: antithrombin, protein C, or protein S deficiency, and double heterozygous, or homozygous factor V Leiden or prothrombin G20210A mutation. Probands: patients with established VTE. *Incidence rates are presented in the Table S1. †Adjusted for clustering within families. ‡Variables included in the multivariable analysis.

indicator for VTE (odds ratio 0.96 [0.67–1.38]) [16]. However, in this study those patients with estrogen-associated VTEs were classified as having unprovoked VTE. It is well possible that the highest risk in relatives of young patients with VTE (age < 45 yrs) as found in this study, is partly explained by an increased risk in female relatives of patients with hormonally (estrogen)-related VTEs (who are inherently young), as observed in our study. In our study, we also evaluated the influence of patient's age at time of first VTE and observed an overall increased risk of VTE in female relatives of younger patients (first VTE < 45 yrs), but in multivariable analyses, influence of patient's age was no longer an independent risk indicator. Although the authors of this study by Couturaud *et al.* [16] indicate that it is possible that inclusion of patients with estrogen-associated VTE among the patients with unprovoked VTE could have diluted the comparison of VTE risk between first-degree relatives of patients with unprovoked vs. provoked VTE, they were unable to assess this directly. Thus, no previous studies with a similar objective are available for comparison.

Our study has its limitations as discussed previously in the separate publications based on these family cohorts [1–3,7,8]. Due to the study design, not all events were established by objective techniques, because these were not yet available at the time. Consequently, the reported absolute risk of VTE may have been overestimated. Further, we were not able to adjust for variables such as BMI, trauma and surgery, as data on these 'temporary' risks were not complete for the whole exposure period. Although we *a priori* defined subgroup analyses, the main

limitation is that results of our analyses are based on small numbers of VTE. All included centers were university hospitals, which could have led to a selection bias of younger and more severe VTE cases. However, in our cohorts, only the probands were referred to the university hospitals. Compared with a Dutch population-based cohort [17], our female probands were indeed younger, but not the male probands (mean age 46 yrs in male and 35 yrs in female probands vs. 49 yrs in male and 43 yrs female cases, respectively). The proportion of PE was not higher than expected (21%). The first-degree relatives of the probands were identified by pedigree analysis, so no selection bias could not have occurred there.

Strong points of our pooled family cohort are the inclusion of consecutive patients with symptomatic VTE and the inclusion of their female relatives who all have confirmed positive family history. Further, extensive efforts made to minimize the recall bias on hormone exposure resulted in an almost complete data collection on exposure to hormone factors during reproductive age, in both female relatives and patients. Moreover, due to the cohort design, we were able to estimate the absolute risk of VTE.

Conclusions

This is the first analysis taking into account a family history, based on a female patient with a hormonally related VTE. Although further research is needed, our findings suggest that a family history originating from a female patient, that is, a mother or sister, especially when that patient experienced a COC- or pregnancy-related VTE may further increase VTE risk in her female relatives. This information could be important in the counseling of women on contraceptive options.

Addendum

E. van Vlijmen and N. Veeger were responsible for the study concept and design. E. van Vlijmen, K. Meijer, and N. Veeger analyzed and interpreted data. Statistical analyses were performed by N. Veeger. E. van Vlijmen wrote the draft manuscript. K. Meijer, N. Veeger, S. Middeldorp, and K. Hamulyák provided input and critical review of the manuscript. All authors approved the final manuscript.

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Disclosure of Conflict of Interests

K. Meijer reports grants and travel support from Baxter; grants, travel support and speaker fees from Bayer and Sanquin; travel support from Pfizer; and speaker fees from Boehringer Ingelheim and Bristol-Myers Squibb, outside the submitted work. S. Middeldorp reports grants and personal fees from GSK, BMS/Pfizer, Aspen and Daiichi Sankyo; grants from Sanquin; and personal fees from Bayer and Boehringer Ingelheim, outside the submitted work.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Venous thromboembolism (VTE) incidence rates in female relatives of all probands, of male probands and female probands, and female probands with or without hormonally related VTE

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